

application was filed, had possession of the claimed invention was maintained. This rejection is respectfully traversed.

The Examiner maintains that the conditions of 37 C.F.R. 1.801-1.809 remain unmet. Applicants disagree. A Statement of Availability concerning the deposit of hybridoma cell line D7 in accordance with the Budapest Treaty and signed by an attorney of record was submitted on May 30, 2002. In addition, the specification was amended on May 30, 2002, by replacement of the paragraph beginning at page 4, line 6, to recite the date of the deposit and the complete name and address of the depository.

The biological deposit was made after the effective filing date of the application, and the Examiner, citing *In re Lundak*, 773 F. 2d 1216, 227 USPQ 90 (CAFC 1985), notes that a verified statement is required from a person in position to corroborate that the deposited hybridomas are producing the monoclonal antibodies as described in the specification as filed and are the same as those deposited in the depository. In response thereto, Applicants submit the Declaration of Michael Kinch, Ph.D., providing the requested corroborative evidence.

It is respectfully submitted that the requirements of 37 C.F.R. 1.801-1.809 are now satisfied. Reconsideration and withdrawal of the rejection of claims 4, 31, 50 and 54 under 35 U.S.C. §112, first paragraph, is respectfully requested.

The Examiner rejected claims 1, 3, 5-13, 21-24, 28-30, 32-47, 49, 51-53, 55-69, 72, 73, 75-81, 90 and 91 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is respectfully traversed.

The Examiner notes that the pending claims are drawn to methods for detecting metastatic cells which are dependent upon the detection of EphA2, and maintains that the specification is insufficient because it does not define EphA2 in terms of sequence or structure. The Examiner states that "[g]iven the broadest reasonable interpretation EphA2 could read on a

genus of tyrosine kinases which are up regulated in metastatic cells comprising proteins expressed from allelic variants, splice variants which have not been disclosed."

Applicants vigorously disagree, and submit that the Examiner has not met the initial burden of, after a thorough reading and evaluation of the content of the application, presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims.

Applicants contend that one of skill in the art would readily recognize that the written description of the invention provides support for the claims. In describing EphA2, the specification states that EphA2 is a "transmembrane receptor tyrosine kinase with a cell-bound ligand" and "[a] member of the Eph family of tyrosine kinases known as Ephrins" (specification at page 2, lines 5-6). The specification further states the EphA2 was cloned a decade ago, and cites Lindberg, R.A. and Hunter, T., "cDNA Cloning and Characterization of Eck, an Epithelial Cell Receptor Protein-tyrosine Kinase in the Eph/elk Family of Protein Kinases," Mol. Cell. Biol. 10 (12), 6316-6324 (1990) (specification at page 2, lines 7-9). The Lindberg et al. publication, which was of record in the present matter in the Information Disclosure Statement submitted February 12, 2001, reports the nucleotide and amino acid sequence of EphA2, at that time referred to as "Eck".

Furthermore, the structure of EphA2 was well-known to the art at the time of the invention. A simple Medline search (attached as Exhibit A) shows 63 papers identified in response to an "EphA2" inquiry, of which 30 were published prior to August, 2000, the month in which the present application was filed.

Finally, the specification describes hybridoma cell lines producing antibodies D7 and B2D6 that bind EphA2 (specification at page 4, lines 6-12). "The D7 antibodies of this invention are highly specific for an intracellular epitope of EphA2" (specification at page 4, lines 24-25). It is well-known that interactions between antibodies and their targets are structurally defined. As noted above and in the Amendment mailed May 30, 2002, these hybridomas have been deposited in accordance with the Budapest Treaty.

Applicants thus contend that the "sequence or structure" of EphA2 is defined in the specification in a manner that provides sufficient support in the context of the invention *as claimed*. Applicants are not claiming EphA2 *per se*, the structure of which was well-known to the art. Rather, Applicants discovered an important relationship between metastatic cancers and EphA2 expression, and as noted by the Examiner are claiming methods that involve, at some point in the method, identification of metastatic cancer cells that express EphA2. The original paper describing EphA2 nucleotide and amino acid sequences was cited in the specification. Antibodies that specifically bind EphA2 are described in the specification and enabled by a Budapest Treaty deposit. EphA2 has been the subject of numerous publications in the scientific literature without recitation of its structure. The reason given by the Examiner for the insufficiency of the specification (i.e., that the term EphA2 could read on a genus of tyrosine kinases that include proteins expressed from "allelic variants" or "splice variants" that have not been disclosed) fails to sustain the Examiner's burden under the Written Description Guidelines. The Examiner has not shown any ambiguity in the literature as to the meaning of the term EphA2.

For at least the foregoing reasons, it is respectfully submitted that the pending claims satisfy the requirements of 35 U.S.C. §112, first paragraph. Reconsideration and withdrawal of the rejection of claims 1, 3, 5-13, 21-24, 28-30, 32-47, 49, 51-53, 55-69, 72, 73, 75-81, 90 and 91 under 35 U.S.C. §112, first paragraph, is respectfully requested.

Information Disclosure Statement mailed May 30, 2002

Applicants note that the Information Disclosure Statement mailed May 30, 2002, has not yet been considered. Applicants request consideration of the documents listed therein and on the accompanying 1449 form(s), and request that an initialed copy of the 1449 form(s) be returned to the Applicants with the next Official Communication. A copy of the 1449 form(s) is provided as Exhibit B.

Information Disclosure Statement mailed December 27, 2001

Applicants note that the Information Disclosure Statement mailed December 27, 2001, has not yet been considered. Applicants request consideration of the documents listed on the accompanying 1449 form(s), and request that an initialed copy of the 1449 form(s) be returned to the Applicants with the next Official Communication. A copy of the 1449 form(s) is provided as Exhibit C.

Information Disclosure Statement mailed October 5, 2001

Applicants note that only one of the two documents submitted with the Information Disclosure Statement mailed October 5, 2001, was considered. Applicants request consideration of the second document listed on the accompanying 1449 form(s), namely Zantek et al., "Chapter 25: Analysis of Cell Migration," in: Methods in Cell Biology 549-559, and request that an initialed copy of the 1449 form(s) be returned to the Applicants with the next Official Communication. A copy of the partially executed 1449 form(s) is provided as Exhibit D.

Supplemental Information Disclosure Statement

Applicants submit herewith a Supplemental Information Disclosure Statement, along with 1449 form(s) and the documents cited thereon. Applicants request consideration of the documents listed on the accompanying 1449 form(s), and request that an initialed copy of the 1449 form(s) be returned to the Applicants with the next Official Communication.

**Amendment and Response**

Page 6 of 14

Serial No.: 09/640,952

Confirmation No.: 3252

Filed: 17 August 2000

For: EPHA2 AS A DIAGNOSTIC TARGET FOR METASTATIC CANCER (As Amended)

**Summary**

It is respectfully submitted that the pending claims 1, 3-13, 21, 23, 24, 28, 30, 31, 33-47, 49-69, 72, 73, 75-81, 90 and 91. are in condition for allowance and notification to that effect is respectfully requested. The Examiner is invited to contact Applicants' Representatives, at the below-listed telephone number, if it is believed that prosecution of this application may be assisted thereby.

Respectfully submitted for  
Purdue Research Foundation

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## **APPENDIX A - PENDING CLAIMS**

**Serial No.: 09/640,952**  
**Docket No.: 290.0009 0101**

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1. A method for detecting the presence of metastatic cells in a cell population comprising the steps of
  - lysing at least a portion of the cell population,
  - incubating the lysed cells with a monoclonal antibody that specifically binds EphA2 to allow antibody binding to EphA2, and
  - detecting antibody-EphA2 binding.
3. The method of claim 2 wherein the epitope of EphA2 is an intracellular epitope of EphA2.
4. The method of claim 3 wherein the antibody is produced by hybridoma cell line D7.
5. The method of claim 2 wherein the antibody is labeled with a detectable label, and the detecting step includes detecting the label.
6. The method of claim 5 wherein the antibody is labeled with a fluorescent label and the detecting step comprises detecting the fluorescent label.
7. The method of claim 5 wherein the antibody is labeled with a radioactive label and the detecting step comprises detecting the radioactive label.
8. The method of claim 1 wherein the cell population comprises cells from a breast or prostate tissue biopsy.
9. The method of claim 1 wherein the cell population is harvested from a body fluid selected from the group consisting of blood, plasma, spinal fluid, saliva, and urine.

10. The method of claim 9 wherein the detecting step includes a diagnostic method selected from the group consisting of ELISA assays and flow cytometry.
11. The method of claim 1 wherein the incubating and detecting steps comprise western blotting methodology.
12. The method of claim 11 further comprising the steps of  
providing a second antibody having phosphotyrosine specificity, and  
western blotting with the second antibody.
13. The method of claim 1 wherein the metastatic cells are selected from the group consisting of breast, prostate, lung, and colon cancers.
21. A method for detecting the presence of metastatic cells in a cell population comprising the steps of  
incubating the cells with a reagent capable of specific binding to a nucleic acid coding for the EphA2 protein, and  
detecting reagent-compound binding.
23. The method of claim 21 wherein the nucleic acid DNA or RNA.
24. The method of claim 21 further comprising the step of fixing the cells on a slide, and the detecting step comprises immunofluorescence staining.
28. The method of claim 1 wherein antibody-EphA2 binding is indicative of the presence of metastatic cells in the cell population.
30. The method of claim 1 wherein the antibody binds to an intracellular epitope of EphA2.

31. The method of claim 1 wherein the antibody is produced by hybridoma cell line D7.
33. The method of claim 5 wherein the antibody comprises at least one of a fluorescent label, a chemiluminescent label, a bioluminescent label, an enzymatic label, a chromogenic label and a radiolabel, wherein detecting reagent-EphA2 binding comprises detecting at least one detectable label.
34. The method of claim 28 wherein the cell population comprises cells selected from the group consisting of breast cells, kidney cells, prostate cells, lung cells and colon cells.
35. The method of claim 28 wherein the cell population comprises epithelial cells.
36. The method of claim 28 wherein the cell population comprises cells selected from the group consisting of breast cancer cells, kidney cancer cells, prostate cancer cells, lung cancer cells and colon cancer cells.
37. The method of claim 28 wherein the cell population comprises epithelial cancer cells.
38. The method of claim 28 wherein the cell population comprises metastatic cancer cells.
39. The method of claim 38 wherein the metastatic cancer cells comprise cells selected from the group consisting of breast cancer cells, kidney cancer cells, prostate cancer cells, lung cancer cells, and colon cancer cells.
40. The method of claim 38 wherein the metastatic cancer cells comprise epithelial cancer cells.
41. The method of claim 28 wherein the cell population comprises cells from a tissue biopsy.



42. The method of claim 41 wherein the tissue comprises breast tissue or prostate tissue.
43. The method of claim 28 wherein the cell population comprises cells from a body fluid.
44. The method of claim 43 wherein the body fluid is selected from the group consisting of blood, plasma, spinal fluid, saliva, and urine.
45. The method of claim 28 wherein detecting antibody-EphA2 binding comprises utilizing a diagnostic method selected from the group consisting of an ELISA assay, a Western blot, and flow cytometry.
46. The method of claim 28 wherein detecting antibody-EphA2 binding comprises utilizing a Western blot; the method further comprising Western blotting with a second antibody having phosphotyrosine specificity.
47. A method for detecting the presence of metastatic cells in a cell population comprising:  
incubating at least a portion of the cell population with a monoclonal antibody that specifically binds EphA2 to allow binding of the antibody to EphA2; and  
detecting antibody-EphA2 binding, wherein antibody-EphA2 binding is indicative of the presence of metastatic cells in the cell population.
49. The method of claim 47 wherein the antibody binds to an intracellular epitope of EphA2.
50. The method of claim 47 wherein the antibody is produced by hybridoma cell line D7.
51. The method of claim 47 wherein the antibody binds to an extracellular epitope of EphA2.

52. The method of claim of claim 47 wherein antibody-EphA2 binding yields a bound complex comprising a whole cell.
53. The method of claim 52 wherein detecting antibody-EphA2 binding comprises subjecting the bound complex to immunohistochemical staining.
54. The method of claim 47 wherein the antibody is produced by hybridoma cell line B2D6.
55. The method of claim 47 wherein the bound antibody comprises a detectable label; and wherein detecting antibody-EphA2 binding comprises detecting the label.
56. The method of claim 47 wherein the bound antibody comprises at least one of a fluorescent label, a chemiluminescent label, a bioluminescent label, an enzymatic label, a chromogenic label and a radiolabel; and wherein detecting antibody-EphA2 binding comprises detecting at least one detectable label.
57. The method of claim 47 wherein the cell population comprises cells selected from the group consisting of breast cells, kidney cells, prostate cells, lung cells and colon cells.
58. The method of claim 47 wherein the cell population comprises epithelial cells.
59. The method of claim 47 wherein the cell population comprises cells selected from the group consisting of breast cancer cells, kidney cancer cells, prostate cancer cells, lung cancer cells and colon cancer cells.
60. The method of claim 47 wherein the cell population comprises epithelial cancer cells.
61. The method of claim 47 wherein the cell population comprises metastatic cancer cells.

62. The method of claim 61 wherein the metastatic cells comprise cells selected from the group consisting of breast cancer cells, kidney cancer cells, prostate cancer cells, lung cancer cells, and colon cancer cells.
63. The method of claim 47 wherein the metastatic cells comprise epithelial cancer cells.
64. The method of claim 47 wherein the cell population comprises cells from a tissue biopsy
65. The method of claim 64 wherein the tissue comprises breast tissue or prostate tissue.
66. The method of claim 47 wherein the cell population comprises cells from a body fluid.
67. The method of claim 66 wherein the body fluid is selected from the group consisting of blood, plasma, spinal fluid, saliva, and urine.
68. The method of claim 47 wherein detecting reagent-EphA2 binding comprises utilizing a diagnostic method selected from the group consisting of an ELISA assay, a Western blot, and flow cytometry.
69. The method of claim 47 wherein detecting reagent-EphA2 binding comprises utilizing a Western blot; the method further comprising Western blotting with a second antibody having phosphotyrosine specificity.
72. A method for detecting the presence of cancer cells in a selected cell population comprising:  
    assaying at least a portion of the selected cell population for at least one of  
        a change in EphA2 intracellular localization pattern; and  
        a change in EphA2 phosphorylation content

as compared to the intracellular localization pattern and phosphorylation content in an analogous normal cell population;

wherein the change is indicative of the presence of a cancer cell in the selected cell population.

73. The method of claim 72 wherein a change in intracellular localization pattern or phosphorylation content is indicative of the presence of metastatic cancer cells in the cell population.

75. The method of claim 72 wherein assaying the cell population comprises incubating at least a portion of the selected cell population with a reagent capable of binding to EphA2 to allow binding of the reagent to EphA2; and detecting reagent-EphA2 binding.

76. The method of claim 75 wherein the reagent is an antibody.

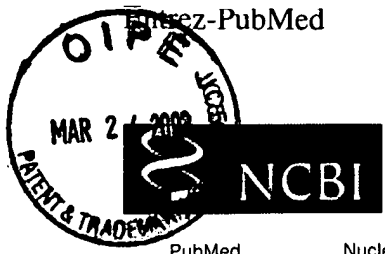
77. The method of claim 76 wherein the antibody is produced by hybridoma D7 or B2D6.

78. A method for determining the disease stage in a cell population comprising cancer cells, the method comprising:

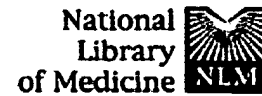
assaying at least a portion of the cell population for at least one of  
EphA2 intracellular localization; and  
EphA2 phosphorylation content; and  
determining the disease stage of the cancer cells.

79. The method of claim 78 wherein assaying the cell population comprises incubating at least a portion of the cancer cell population with a reagent capable of binding to EphA2 to allow binding of the reagent to EphA2; and detecting reagent-EphA2 binding.

80. The method of claim 79 wherein the reagent is an antibody.
81. The method of claim 80 wherein the antibody is produced by hybridoma D7 or B2D6.
90. A method for detecting the presence of cancer cells in a selected cell population comprising:
- assaying at least a portion of the selected cell population for at least one of
    - a change in EphA2 expression level;
    - a change in EphA2 intracellular localization pattern; and
    - a change in EphA2 phosphorylation content
  - as compared to the EphA2 expression level, intracellular localization pattern and phosphorylation content in an analogous normal cell population;
  - wherein the assaying the cell population comprises incubating at least a portion of the selected cell population with a monoclonal antibody, and wherein the change is indicative of the presence of a cancer cell in the selected cell population.
91. The method of claim 82 wherein a change in EphA2 expression level is indicative of the presence of nonmetastatic cancer cells in the cell population.



#23



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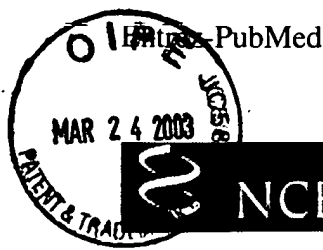
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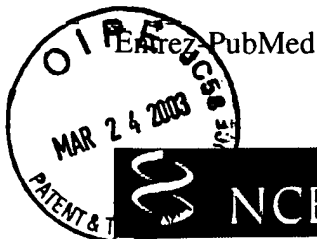
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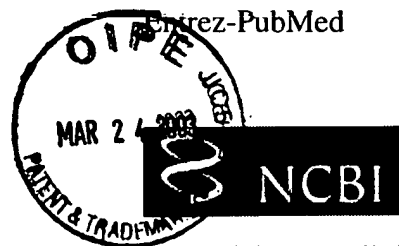
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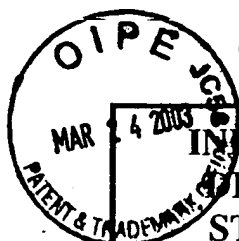
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